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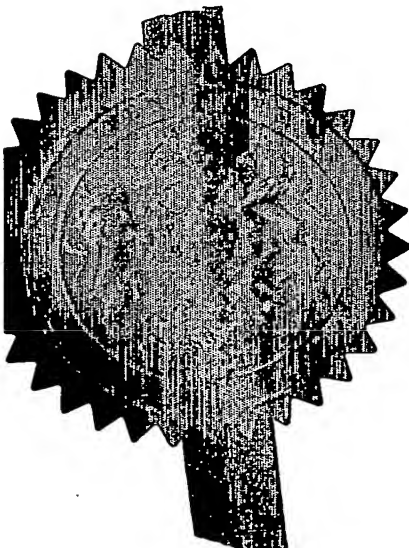
PCT

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Signed *Andrew Gurney*
Dated 22 April 2004

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ITT0055PV

Patent application number
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0307891.2

07APR03 E798047-1 002639
P01/7700 0.00-0307891.2

Full name, address and postcode of the or of each applicant (underline all surnames)

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557036002

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

Title of the invention

Chemical compounds, compositions and uses

Name of your agent (if you have one)

Dr. W. G. Cole

Address for service" in the United Kingdom which all correspondence should be sent including the postcode)

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Terlings Park
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Essex CM20 2QR

Patents ADP number (if you know it)

01010289001

01010529002

If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority Application number
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Date of filing
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If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

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Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

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I/We request the grant of a patent on the basis of this application.

Signature

Dr. W. G. Cole

Date 04 April 2003

Name and daytime telephone number of person to contact in the United Kingdom

Dr. W. G. Cole

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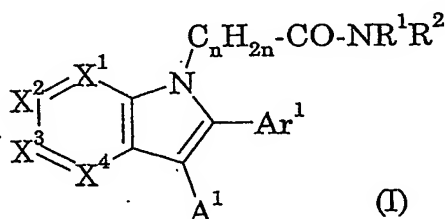
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CHEMICAL COMPOUNDS, COMPOSITIONS AND USES

The present invention relates to indole and azaindole compounds, to pharmaceutical compositions containing them, to their use in the prevention and treatment of hepatitis C infections and to methods of preparation of such compounds and compositions.

Hepatitis C (HCV) is a cause of viral infections. There is as yet no adequate treatment for HCV infection but it is believed that inhibition of its RNA polymerase in mammals, particularly humans, would be of benefit. International patent applications WO 01/47883, WO 02/04425 and WO 03/000254 suggest fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible benzimidazole derivatives that possess HCV polymerase inhibitory properties. However, these patent applications do not describe or reasonably suggest the preparation of any benzimidazole or azabenzimidazole substituted on all three available sites on the fused imidazole ring. WO 03/010140 and WO 03/010141 suggest further fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible compounds all of which possess complex esterified side chains. The corresponding acids are suggested as intermediates only and not as HCV polymerase inhibitors. In particular none of these patent applications describe an indole or azaindole in which the indole nitrogen is substituted by an alkylamide residue.

The present invention provides compounds of the formula (I):



wherein:

- Ar¹ is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which may be N, O or S heteroatoms of which at most 1 will be O or S; which moiety may be optionally substituted by groups Q₁, Q₂ or Q₃ wherein Q₁ is a hydroxy group, or a hydrogen, fluorine, chlorine, bromine or iodine atom or a C₁₋₆ alkyl, C₁₋₆ alkyl substituted by not more than 5 fluorine atoms, C₁₋₆ alkoxy, C₁₋₆ alkoxy substituted by not more than 5 fluorine atoms, C₂₋₆ alkenyl or alkynyl, nitro, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms, Q₂ is a fluorine or chlorine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxy or difluoromethoxy group. Q₃ is a fluorine or chlorine atom or a methyl, methoxy, trifluoromethoxy or difluoromethoxy group; or Ar¹ is a group disclosed as a substituent on the G⁶ moiety of the compound of formula (I) of WO 01/47883 which is incorporated herein by cross reference;
- X¹ is N or CR^a; X² is N or CR³; X³ is N or CR⁴; X⁴ is N or CR^b; with the proviso that at least one of X² and X³ is not N; wherein R^a and R^b are independently selected from hydrogen, fluorine or chlorine or C₁₋₄alkyl, C₂₋₄alkenyl, C₁₋₄alkoxy, C₁₋₄alkyl or alkoxy optionally substituted by up to 6 fluorine atoms and/or a hydroxyl group;
- n is 1, 2, 3, 4, 5 or 6;
- R¹ and R² are independently hydrogen, a group Ar², C₁₋₆ alkyl, C₂₋₆ alkenyl or a C₁₋₆ alkyl or C₂₋₆ alkenyl group substituted by 1-3 fluorine atoms or a OR⁷, NR⁷R⁸, CO₂H, Ar² or A² group or R¹ and R² are joined to form a ring of 3 to 8 ring atoms, 1 or 2 of which ring atoms may be selected from N, O, S, SO, or SO₂ moieties, which ring may be substituted by a group Ar², A², C₁₋₆ alkyl, C₁₋₆ alkyl Ar², C₁₋₆ alkyl

A², or a further ring of 5-6 ring atoms 1 or 2 of which may be selected from N, O, S which further ring may be substituted by C₁₋₆ alkyl substituted by 1-3 fluorine atoms, OR⁷, NR⁷R⁸ or CO₂H group; R⁷ is hydrogen or C₁₋₆ alkyl, R⁸ is hydrogen, C₁₋₄ alkyl optionally substituted by hydroxy, carboxy, amino, monoC₁₋₆ alkyl or diC₁₋₆ alkyl wherein the alkyl groups may be joined to form a 5- or 6-membered unsaturated ring which may contain a O, S, NH or NCH₃ group;

Ar² is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which atoms may be N, O or S heteroatoms of which at most 1 will be O or S; which aromatic ring may be optionally substituted by groups Q₁['], Q₂['] or Q₃['] wherein Q₁['] is a hydroxy group, or a hydrogen, fluorine, chlorine, bromine or iodine atom or a C₁₋₆ alkyl, C₁₋₄ alkyl substituted by not more than 5 fluorine atoms, C₁₋₆ alkoxy, C₁₋₄ alkoxy substituted by not more than 5 fluorine atoms, C₂₋₆ alkenyl or alkynyl, nitro, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms,

Q₂['] is a fluorine or chlorine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxy or difluoromethoxy group.

Q₃['] is a fluorine or chlorine atom or a methyl, methoxy, trifluoromethoxy or difluoromethoxy group;

A¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₁₋₆ alkyl or C₂₋₆ alkenyl substituted by C₁₋₄ alkoxy or up to 5 fluorine atoms or a non-aromatic ring of 3 to 8 ring atoms which may contain a double bond and which may contain a O, S, SO, SO₂ or NH moiety and which may be optionally substituted by one or two alkyl groups of up to 2 carbon atoms or by 1 to 8 fluorine atoms;

A² is C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₁₋₆ alkyl or C₂₋₆ alkenyl substituted by C₁₋₄ alkoxy or up to 5 fluorine atoms or a non-aromatic ring of up to

8 ring atoms which may contain a double bond and which may contain a O, S, SO, SO₂ or NH moiety and which may be optionally substituted by one or two alkyl groups of up to 2 carbon atoms or by 1 to three fluorine atoms;

- 5 one of R³ and R⁴ is a Het or is hydrogen, fluorine, chlorine or bromine atom or a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₁₋₄ alkoxy, C₁₋₄ alkyl or alkoxy substituted by up to 5 fluorine atoms, nitrile, carboxy, C₁₋₄ alkoxycarbonyl, C₁₋₄ alkyl or C₂₋₄ alkenyl substituted by a carboxy or C₁₋₄ alkoxycarbonyl group, or a SO₂NR⁹R¹⁰ or CONR⁹R¹⁰ group
10 where R⁹ is hydrogen, C₁₋₄ alkyl, SO₂R¹¹ or COR¹¹ and R¹⁰ is hydrogen, hydroxyl or C₁₋₄ alkyl or R⁹ and R¹⁰ are alkylene linked to form a 5- or 6-membered ring, and R¹¹ is C₁₋₄ alkyl optionally substituted by up to 5 fluorine atoms or a group independently chosen from within the definitions of the Ar² group;
15 Het is a 5 or 6-membered aromatic ring 1, 2 or 3 of which may be selected from N, O, S which ring may be substituted by 1 or 2 groups selected C₁₋₄ alkyl or hydroxy or tautomers thereof, or is 2-hydroxy-cyclobutene-3,4-dione;
the other of R³ and R⁴ is a hydrogen, fluorine or chlorine atom or C₁₋₄ alkyl,
20 C₂₋₄ alkenyl, C₁₋₄ alkoxy, C₁₋₄ alkyl or alkoxy substituted by up to 6 fluorine atoms and optionally a hydroxyl; and
or a pharmaceutically acceptable salt thereof.

- The group C_nH_{2n} may be straight or branched such as a -CH₂-, -
25 (CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -CH(CH₃)-, -CH₂-CH(CH₃)-, -CH(CH₃)-CH₂- or the like straight or branched butyl, pentyl or hexyl group. Most suitably the C_nH_{2n} group is a -CH₂- group.

- When used herein C₁₋₆ alkyl means methyl, ethyl, 1-propyl, 2-propyl
30 or a straight or branched butyl, pentyl or hexyl group. Particularly apt

C₁₋₆ alkyl groups are methyl, ethyl, propyl and butyl groups. Favoured

alkyl groups are ethyl and methyl groups. The methyl group is the preferred alkyl group.

Most suitably a C₁₋₆ alkyl group substituted by up to 5 fluorine atoms will include a CF₃, CHF₂ and/or CF₂ moiety. Favoured fluoroalkyl groups are the CF₃, CH₂F and CF₂CF₃ groups. The CF₃ group is the preferred fluoroalkyl group.

When used herein C₂₋₆ alkenyl means a -CH=CH₂, -C(CH₃)=CH₂, -CH=C(CH₃), -C(CH₃)=C(CH₃) or straight or branched pentylene or hexylene groups.

When used herein C₁₋₆ alkoxy and fluorinated C₁₋₆ alkoxy are analogous to the alkyl and fluoroalkyl groups described above so that, for example, preferred groups include OCH₃, OCF₃ and OCHF₂ groups.

Favoured values for R^a and R^b independently include hydrogen, fluorine, methyl, methoxy and trifluoromethyl. Particularly apt values for R^a and R^b include hydrogen or fluorine. A preferred value for R^a is hydrogen. A preferred value for R^b is hydrogen.

The Ar¹ moiety may contain a single aromatic ring or one aromatic ring to which a further aromatic or non-aromatic ring is fused.

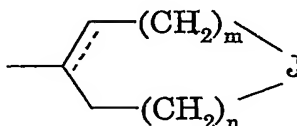
Ar¹ is aptly phenyl, naphthyl, indinyl, tetrahydronaphthyl, pyridyl, furyl, thienyl, pyrolidyl, oxazolyl, thiazolyl, pyrazolyl, pyridazolyl, triazolyl, oxadiazolyl, thiodiazolyl or quinonyl, any of which may be optionally substituted by group Q¹, Q² or Q³ as hereinbefore defined.

Favourably, Ar¹ is a furyl or thienyl group or a group of the formula C₆H₂Q¹Q²Q³. One particularly favoured group Ar¹ is the furyl group,

Other particularly favoured Ar^1 groups are optionally substituted phenyl groups of the formula $\text{C}_6\text{H}_3\text{Q}^1\text{Q}^2$ of which phenyl, fluorophenyl, chlorophenyl, hydroxyphenyl, trifluoromethylphenyl, methoxyphenyl, difluorophenyl and the like are preferred.

5

Particularly suitable groups A^1 include those groups of the formula



10 wherein $m + n$ is 0, 1, 2, 3 or 4, preferably 1 or 2, the dotted line represents an optional double bond and J is CH_2 , O, S, SO, SO_2 or NH which group of the above formula may optionally be substituted by one or two methyl groups.

15 Favoured groups A^1 include cycloalkyl and cycloalkenyl groups of 5 or 6 ring members.

A preferred group A^1 is the cyclohexyl group.

20 Particularly apt compounds of this invention include those wherein one of R^3 and R^4 is a carboxy or $-\text{Y}-\text{CO}_2\text{H}$ group wherein Y is CH_2 , CH_2CH_2 or $\text{CH}:\text{CH}$ group, or a pharmaceutically acceptable salt thereof.

A preferred group R^3 is the CO_2H group or a pharmaceutically acceptable
25 salt thereof.

Favourably one of R^3 and R^4 is a hydrogen atom.

Certain favoured compounds of the invention include those wherein R^4 is hydrogen, fluorine or chlorine of which hydrogen is preferred.

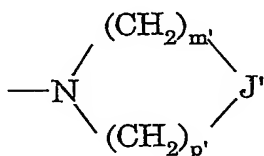
A favoured value for X_4 is CH.

5

In those compounds of formula (I) wherein R^1 is a hydrogen atom or C_{1-4} alkyl group R^2 may aptly be a hydrogen atom or a C_{1-4} alkyl or a group C_{1-4} alkyl Ar^2 group wherein the Ar^2 group is as hereinbefore defined wherein Q^2 and Q^3 are hydrogen atoms.

10

In those compounds of formula (I) wherein R^1 and R^2 are linked they aptly form an optionally substituted ring of the formula:



15

wherein J' is CH_2 , NH, O, S, SO, or SO_2 and $m' + p'$ is 1 to 6, more aptly 2 to 5 and preferably 3 or 4 and where the one or two optional substituents are selected from C_{1-4} alkyl and hydroxy and Ar^2 where the Ar^2 group is as hereinbefore defined or a fused pendent or spiro 5 or 6 membered ring in which one of the ring moieties may be a O, NH or NCH_3 group.

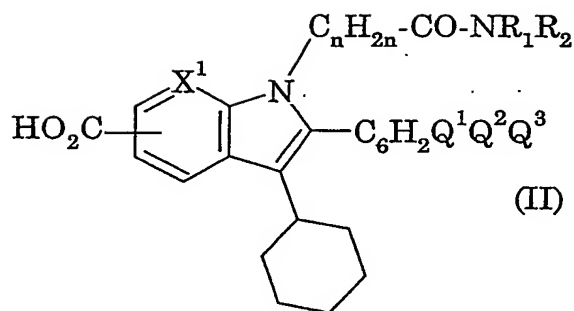
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Favoured values for A^1 include non-aromatic rings. Such rings are aptly of 5 or 6 carbon atoms and which are saturated or monounsaturated.

Preferred groups A^1 include cyclopentyl, cyclohexyl and cyclohexenyl

25 groups.

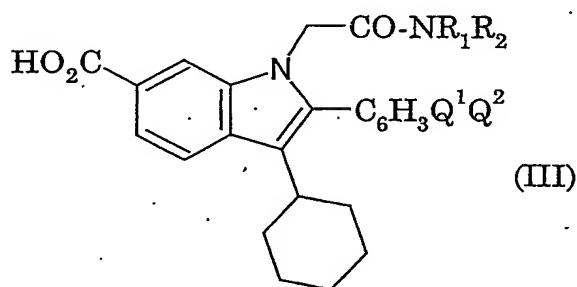
Certain particularly suitable compounds of the invention are represented by the formula (II):



wherein n, X¹, Q¹, Q², Q³, R¹ and R² are as defined in relation to formula (I) or a pharmaceutically acceptable salt thereof.

5

In compounds of formula (I) and (II) a favoured value for Q³ is H, a favoured value for n is 1 and a favoured value for X¹ is CH so that particularly apt compounds of the invention include those of formula (III):



10

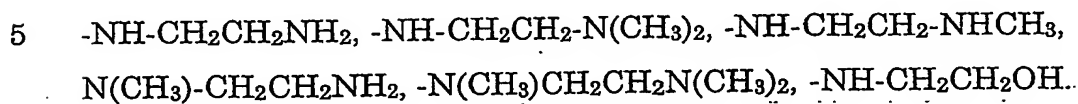
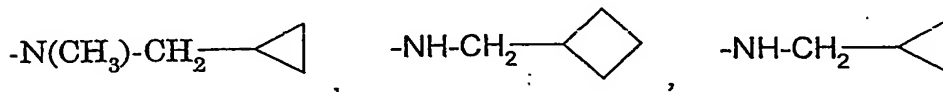
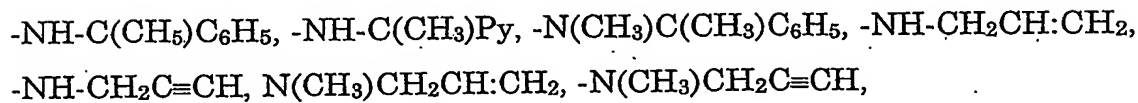
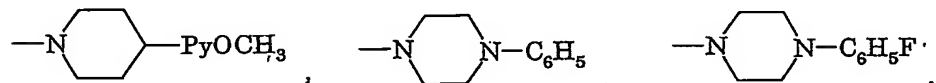
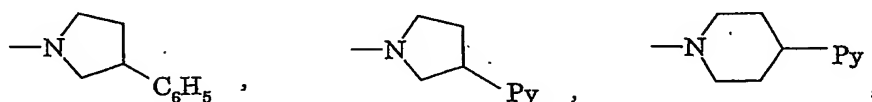
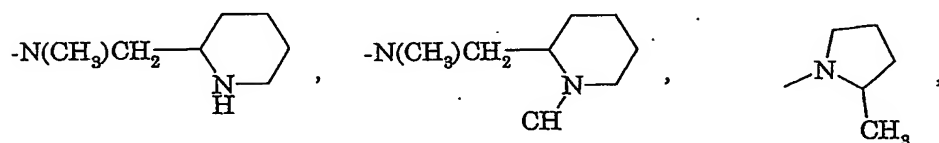
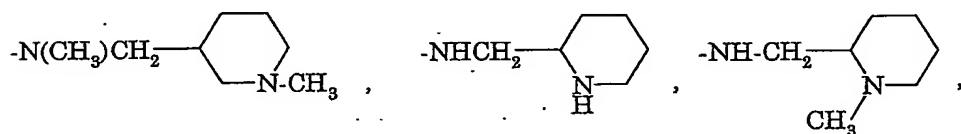
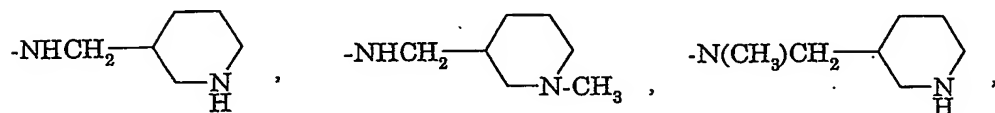
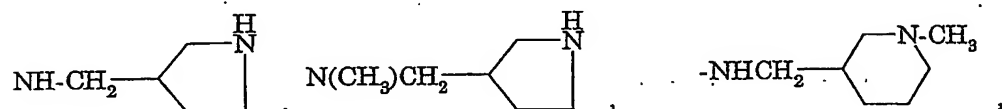
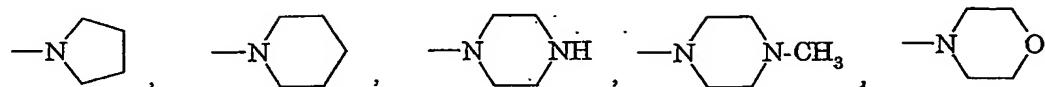
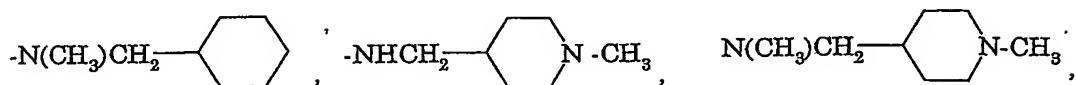
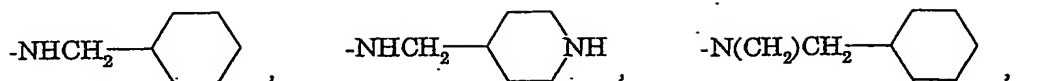
wherein Q¹, Q², R¹ and R² are defined in relation to formula (I) or a pharmaceutically acceptable salt thereof.

15 In certain apt compounds of formulas (II) and (III) Q² is hydrogen fluorine chlorine, methyl, methoxyl or trifluoromethyl. In certain apt compounds of formulas (II) and (III) Q¹ is hydrogen or fluorine. In certain preferred compounds of formulas (II) and (III) Q¹ is hydrogen and Q² is hydrogen or fluorine.

20

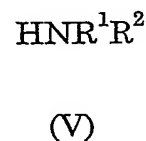
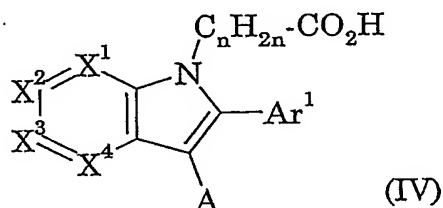
In compounds of formulae (I), (II) and (III) particularly apt values for NR^1R^2 are those wherein R^1 is hydrogen or methyl, R^2 is hydrogen, methyl or ethyl optionally substituted by (i) an aryl group of 5 or 6 ring atoms up to 3 of which may be selected from O, N or S of which not more than one
5 may be O or S which aryl group may be substituted by a methyl or methoxy group; (ii) a 5 or 6 membered saturated ring which one ring atom may be a O, S or N atom and which ring may be substituted by a methyl group; or (iii) 2-substituted by a hydroxy, amino, methylamino or dimethylamino group; or R^1 and R^2 may be joined so that NR^1R^2 forms a 4
10 or 6 membered saturated ring of which one additional ring atom may be a O, S or N atom and which ring may be substituted by a methyl group.

In compounds of formulae (I), (II) and (III) particularly suitable $-NR^1R^3$ groups include (wherein Py is pyridyl):
15 $-NH_2$, $-NH-CH_3$, $-NH-C_2H_5$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-NHCH_2C_6H_5$,
 $-NH-CH_2C_6H_4F$, $-NH-CH_2C_6H_4OCH_3$, $-N(CH_3)CH_2C_6H_5$,
 $-N(CH_3)CH_2C_6H_4F$, $-N(CH_3)CH_2C_6H_4OCH_3$,



The compounds of the formula (I) may be in the form of a pharmaceutically acceptable salt such as a sodium, potassium, calcium, magnesium or ammonium salt or a salt with a pharmaceutically acceptable organic base. If the compounds of the formula (I) also contain a group, the compound
 5 may be zwitterionic or in the form of a salt with a pharmaceutically acceptable acid such as hydrochloric, sulphuric, phosphoric, methane sulfonic and the like acid.

The present invention provides a process for the preparation of compounds
 10 of formula (I) and their salts which comprises the reaction of compounds of the formulas (IV) and (V):

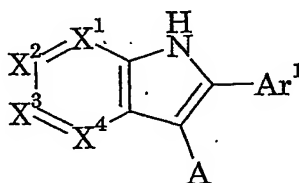


15 In the compounds of formulae (IV) and (V) any reactions group that requires masking during the amidation reaction may be protected in conventional manner and the protecting group removed thereafter.

This principle of utilising protecting groups also applies to all other
 20 reactions described hereinafter. For example, if the desired compound of the formula I contains a CO₂H group, then the compound of the formula (IV) may contain a CO₂CH₃ group and the resulting compound of the formula (I) may be hydrolysed in conventional manner, for example with sodium hydroxide in aqueous methanol or BBr₃ in DCM to yield the
 25 compound containing the carboxylate or its sodium salt. Similarly the substituents on the core bicycle may be elaborated after the amidation reaction, for example if the desired compound of formula (I) contains a

tetrazole group then the compound of formula (IV) may contain CN group and the resulting compound of formula (I) may be reacted with an azide.

5 The compound of the formula (IV) may be prepared from the corresponding compound of the formula (VI):

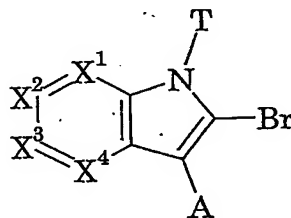


(VI)

10 by reaction with 1-bromo ethanoic acid t-butyl ester under conventional conditions for forming an amide followed by de-esterification with trifluoroethanoic acid in DCM.

In an alternative process the compounds of formula (I) may be prepared from the corresponding compound of the formula (VII):

15

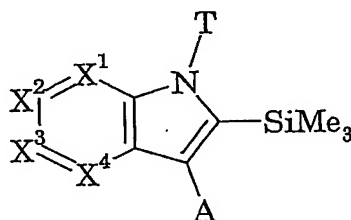


(VII)

wherein T is a C_nH_{2n}CONR¹R² group by reaction with Ar¹B(OH)₂ in the presence of a Pd[O] catalyst under conditions conventional for the Suzuki
20 reaction.

The compound of formula (VII) wherein T is a $C_nH_{2n}CONR^1R^2$ group can be prepared from the compound of formula (VII) wherein T is a hydrogen atom by reaction with 1-bromoethanoic acid t-butyl ester.

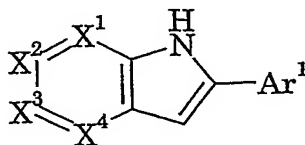
- 5 Alternatively the compound of formula (VII) may be prepared by the reaction of NBS and the compound of the formula (VIII):



(VIII)

- 10 wherein T is $C_nH_{2n}CONR^1R^2$ which may itself be prepared from the corresponding compound of formula (VIII) wherein T is H by reaction with $BrC_nH_{2n}CONR^1R^2$ under conventional alkylation conditions.

- 15 In an alternative synthesis the compounds of the formula (VI) may be prepared from the reaction of corresponding compounds of the formulae (IX) and (X):

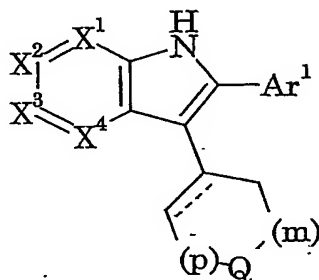


(IX)

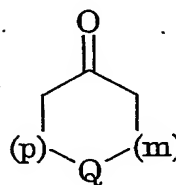


(X)

Similarly certain compounds of the formula (XI) may be prepared by the reaction of a compound of the formula (IX) with compounds of the formula (XII):



(XI)



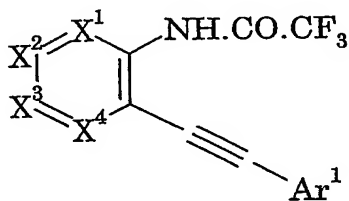
(XII)

5

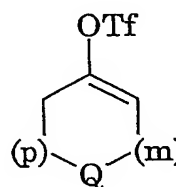
wherein Q is CH₂, NH, O, S, SO or SO₂ and m + p is 1 or 2 and where one or two optional substituents are selected from C₁₋₆ alkyl and hydroxyl and the dotted line is an optional double bond; optionally followed by reduction of said optional double bond.

10

The compounds of formula (XI) may also be prepared by the reaction of the compounds of the formulae (XIII) and (XIV):



(XIII)

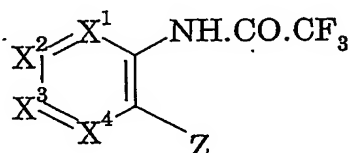


(XIV)

15

wherein Q, m and p are as defined in relation to formula (XII) in the presence of a Pd[O] catalyst optionally followed by reduction of the optional double bond.

The compound of the formula (XIII) may be prepared from the compounds of the formulae (XV) and (XVI):



(XV)

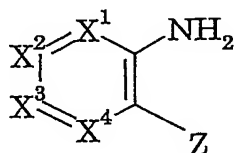


(XVI)

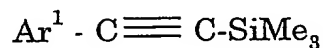
5

wherein Z is I, Br or OTf in the presence of a Pd[O] catalyst.

10 A further process for the preparation of the compounds of formula (VIII) wherein T is hydrogen comprises the reaction of the compounds of the formulae:



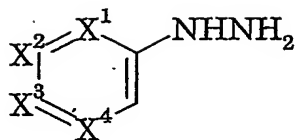
(XVII)



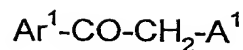
(XVIII)

15 wherein Z is I, Br or OTf.

In addition, compounds of the formula (VI) may be prepared by the reaction of a hydrazine of the formula (XIX):



(XIX)



(XX)

and a ketone of the formula (XX).

- 5 The compounds of formulas (I)-(III) may be used for the inhibition of HCV polymerase and so may be used for the manufacture of medicaments which may be used to treat HCV infection.

- Accordingly this invention provides a pharmaceutical composition
10 comprising a compound of the formula (I) as hereinbefore described as a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

- The invention also provides pharmaceutical compositions
15 comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral,
20 parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical
25 diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a

pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of infection due to hepatitis C, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day. Most suitably the administration is orally using a unit dose as previously indicated.

In a further aspect this invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of infection by hepatitis C

virus. Most suitably the medicament is in unit dose form adapted for oral administration as indicated hereinbefore.

In another aspect this invention provides the use of a compound of
5 Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of infection by hepatitis C virus in a mammal and preferably in a human. Most suitably the treatment is effected by oral administration of a unit dose form as indicated hereinbefore.

10 Useful references in the literature for synthetic preparations include: . . .
Nanomoto et al, J. Chem. Soc. Perkin I, 1990, III; Freter, J. Org. Chem., 1975, 40, 2525; Cacchi et al, Eur. J. Org. Chem., 2002, 2671; Ujjainwalla, Tetrahedron Lett., 1998, 39, 5355; Wang et al, J. Org. Chem., 2000, 65, 1889; Larock, J. Org. Chem., 1998, 63, 7652; Kelly et al, J. Org. Chem.,
15 1996, 61, 4623; and Cacchi, Tetrahedron Lett., 1992, 33, 3915.

The following Examples are illustrative of this invention.

The compounds of the invention were tested for inhibitory activity against the HCV
20 RNA dependent RNA polymerase (NS5B) in an enzyme inhibition assay (example i)) and an cell based sub-genomic replication assay (describe in example ii)). The compounds generally have IC₅₀'s below 5 μ M in the enzyme assay and EC₅₀'s below 20 μ M in the cell based assay. For example -(2-{methyl[(1-methylpiperidin-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate
25 had an IC₅₀ of 14 nM in the enzyme assay and an EC₅₀ of 270 nM in the cell based assay.

i) In-vitro HCV NS5B Enzyme Inhibition Assay

30 WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme.
The purified enzyme was shown to possess *in vitro* RNA polymerase

activity using RNA as template. The reference describes a polymerisation assay using poly(A) and oligo(U) as a primer or an heteropolymeric template. Incorporation of tritiated UTP or NTPs is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (50 µl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM MgCl₂, 1 mM DTT, 50 mM NaCl, 0.03% N-octylglucoside, 1 µCi [³H]-UTP (40 Ci/mmol, NEN), 10 µM UTP and 10 µg/ml poly(A) or 5µM NTPs and 5µg/ml heteropolymeric template. Oligo(U)₁₂ (1 µg/ml, Genset) was added as a primer in the assay working on Poly(A) template. The final NS5B enzyme concentration was 5 nM. The order of assembly was: 1) compound, 2) enzyme, 3) template/primer, 4) NTP. After 1 h incubation at 22 °C the reaction was stopped by adding 50 µl of 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5% TCA containing 1M Na₂HPO₄/NaH₂PO₄, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. Carrying out this reaction in the presence of various concentrations of each compound set out above allowed determination of IC₅₀ values by utilising the formula:

$$\% \text{ Residual activity} = 100/(1+[I]/IC_{50})^s$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

ii) Cell based HCV Replication Assay

Cell clones that stably maintain subgenomic HCV replicon were obtained by transfecting Huh-7 cells with an RNA replicon identical to I₃₇₇neo/NS3-3'/wt described by Lohmann *et al.* (1999) (EMBL-genbank No. AJ242652),

followed by selection with neomycin sulfate (G418). Viral replication was monitored by measuring the expression of the NS3 protein by an ELISA assay performed directly on cells grown in 96 wells microtiter plates (Cell-ELISA) using the anti-NS3 monoclonal antibody 10E5/24 (as described by
5 *De Francesco, Raffaele; Migliaccio, Giovanni; Paonessa, Giacomo. Hepatitis C virus replicons and replicon enhanced cells. PCT Int. Appl. WO 0259321 A2 20020801*). Cells were seeded into 96 well plates at a density of 10^4 cells per well in a final volume of 0.1 ml of DMEM/10% FCS. Two hours after plating, 50 μ l of DMEM/10% FCS containing a 3x
10 concentration of inhibitor were added, cells were incubated for 96 hours and then fixed for 10' with ice-cold isopropanol. Each condition was tested in duplicate and average absorbance values were used for calculations. The cells were washed twice with PBS, blocked with 5% non-fat dry milk in PBS + 0.1% Triton X100 + 0.02% SDS (PBSTS) and then incubated o/n
15 at 4^o C with the 10E5/24 mab diluted in Milk/PBSTS. After washing 5 times with PBSTS, the cells were incubated for 3 hours at room temperature with Fc specific anti-mouse IgG conjugated to alkaline phosphatase (Sigma), diluted in Milk/PBSTS. After washing again as
20 above, the reaction was developed with p-Nitrophenyl phosphate disodium substrate (Sigma) and the absorbance at 405/620 nm read at intervals. For calculations, we used data sets where samples incubated without inhibitors had absorbance values comprised between 1 and 1.5. The inhibitor concentration that reduced by 50% the expression of NS3 (IC₅₀) was calculated by fitting the data to the Hill equation,

25
$$\text{Fraction inhibition} = 1 - (A_i - b) / (A_0 - b) = [I]^n / ([I]^n + IC_{50})$$

where:

- A_i = absorbance value of HBI10 cells supplemented with the indicated inhibitor concentration.
- A_0 = absorbance value of HBI10 cells incubated without inhibitor.
- 30 - b = absorbance value of Huh-7 cells plated at the same density in the same microtiter plates and incubated without inhibitor.

- n = Hill coefficient.

iii) General Procedures

5 All solvents were obtained from commercial sources (Fluka, puriss.) and were used without further purification. With the exception of routine deprotection and coupling steps, reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware. Organic extracts were dried over sodium sulfate, and were concentrated (after filtration of the drying agent) on rotary evaporators operating under reduced pressure. Flash chromatography
10 was carried out on silica gel following published procedure (W.C. Still *et al.*, J. Org. Chem. 1978, 43, 2923) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster) utilising pre-packed columns.

15 Reagents were usually obtained directly from commercial suppliers (and used as supplied) but a limited number of compounds from in-house corporate collections were utilised. In the latter case the reagents are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

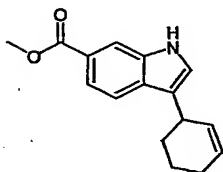
¹H nmr spectra were recorded on Bruker AM series spectrometers
20 operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity
25 (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, and combinations thereof); coupling constant(s) in hertz; number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100 operating in negative (ES⁻) or positive (ES⁺) ionization mode and results are reported as the ratio of mass over charge (m/z) for the parent ion only.
30 Preparative scale HPLC separations were carried out on a Waters Delta Prep 4000 separation module, equipped with a Waters 486 absorption

detector or on a Thermoquest P4000 equipped with a UV1000 absorption detector. In all cases compounds were eluted with linear gradients of water and acetonitrile both containing 0.1% TFA using flow rates between 15 and 25 mL/min.

5 The following abbreviations are used in the examples, the schemes and the tables:

DIEA: diisopropylethyl amine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; eq.: equivalent(s); AcOEt: ethyl acetate; Et₂O: diethyl ether; MeCN: acetonitrile; h: hour(s); HATU: O-(7-azabenzotriazol-1-yl)-
10 *N,N,N',N'*-tetramethyluronium hexafluorophosphate; Me: methyl; EtOH: ethanol; min: minutes; NBS: *N*-bromo succinimide; Ph: phenyl; HPLC: reversed phase high-pressure liquid chromatography; TFA: trifluoroacetic acid; THF: tetrahydrofuran; MeOH: methanol; DME: Ethylene glycol dimethyl ether; TMS: trimethylsilyl.

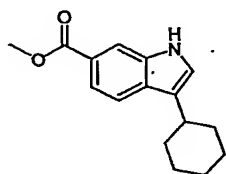
15 **Example 1 : 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid**



20 Step 1: methyl 3-cyclohex-2-en-1-yl-1*H*-indole-6-carboxylate

A solution (0.2 M) of methyl 1*H*-indole-6-carboxylate in DMF was cooled to 0 °C then treated with LiH (1.3 eq.). The mixture was stirred for 0.5 h then warmed to 20 °C. A solution (1.0 M) of 3-bromocyclohex-1-ene (1.5 eq.) in DMF was added and the mixture was stirred for 16 h. AcOEt and H₂O were added and the organic layer
25 was separated then washed with aqueous HCl (1 N) and dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (52%) as an oil.

¹H NMR (300 MHz, CDCl₃, 300 K) δ 1.61-1.85 (m, 4H), 2.05-1.18 (m, 2H), 3.71-3.75 (m, 1H), 3.94 (s, 3H), 5.80-5.95 (m, 2H), 7.14 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 8.20 (br s, 1H); MS (ES⁺) *m/z* 256 (M+H)⁺



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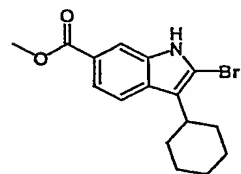
Step 2: methyl 3-cyclohexyl-1H-indole-6-carboxylate

A solution (0.2 M) of methyl 3-cyclohex-2-en-1-yl-1H-indole-6-carboxylate in MeOH was treated with 10% Pd/C (10% wt.). The resulting suspension was stirred for 4 h under an atmosphere of hydrogen then purged with nitrogen and filtered. The filtrate was concentrated to afford the title compound (97%) as a solid.

10

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.22-1.24 (m, 2H), 1.39-1.51 (m, 3H), 1.69-1.81 (m, 3H), 1.95-2.00 (m, 2H), 2.75-2.81 (m, 1H), 3.83 (s, 3H), 7.33 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 11.16 (br s, 1H); MS (ES⁺) *m/z* 258 (M+H)⁺

15



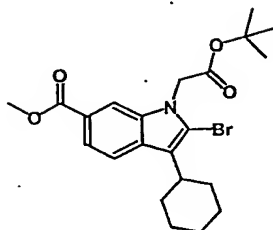
Step 3: methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate

A solution (0.1 M) of methyl 3-cyclohexyl-1H-indole-6-carboxylate in CCl₄, was treated with NBS (1.1 eq.). The resulting mixture was stirred at 40 °C for 2 h, then the reaction was quenched by addition of 10% aqueous Na₂S₂O₄. The organic phase was separated and washed with brine, then dried. Removal of the solvent afforded a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (54%) as a solid.

20

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.32-1.49 (m, 3H), 1.64-2.00 (m, 7H), 2.73-2.88 (m, 1H), 3.84 (s, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 12.02 (br s, 1H); MS (ES⁺) *m/z* 336 (M+H)⁺

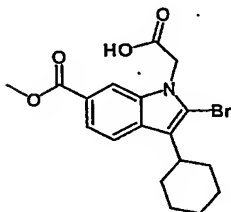
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Step 4: methyl 2-bromo-1-(2-tert-butoxy-2-oxoethyl)-3-cyclohexyl-1H-indole-6-carboxylate

A solution (0.1 M) of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate in
 5 DMF was treated with NaH (1.3 eq.) and stirred for 0.5 h at 0 °C. The solution was
 warmed to room temperature and treated with *tert*-butylbromoacetate (1.2 eq.) over
 0.5 h. The mixture was stirred for 12 h then diluted with AcOEt and washed
 sequentially with aqueous HCl (1 N) and brine. The dried organic phase was
 concentrated and the residue purified by flash chromatography on silica gel (5:95
 10 AcOEt/petroleum ether) to afford the title compound (83%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.31-1.50 (m, 3H), 1.40 (s, 9H), 1.64-1.80
 (m, 3H), 1.81-2.04 (m, 4H), 2.80-2.92 (m, 1H), 3.86 (s, 3H), 5.09 (s, 2H), 7.66 (d, *J* =
 8.4 Hz, 1H); 7.82 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H); MS (ES⁺) *m/z* 452 (M+H)⁺

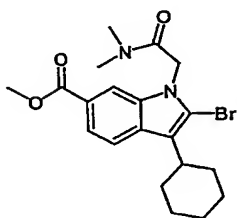


15

Step 5: [2-bromo-3-cyclohexyl-6-(methoxycarbonyl)-1H-indol-1-yl]acetic acid

A solution (0.05 M) of methyl 2-bromo-1-(2-tert-butoxy-2-oxoethyl)-3-cyclohexyl-
 1H-indole-6-carboxylate in a 1:1 mixture of CH₂Cl₂/TFA was stirred for 16 h. The
 20 mixture was concentrated and the residue triturated with Et₂O to afford the title
 compound (95%) as a solid.

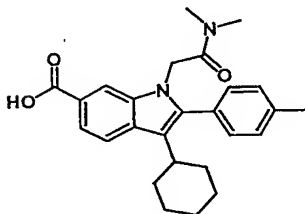
¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.30-1.50 (m, 3H), 1.64-1.78 (m, 3H), 1.79-
 2.02 (m, 4H), 2.79-2.90 (m, 1H), 3.86 (s, 3H), 5.10 (s, 2H), 7.67 (d, *J* = 8.4 Hz, 1H),
 7.83 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H)



Step 6: methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate

A solution (0.2 M) of [2-bromo-3-cyclohexyl-6-(methoxycarbonyl)-1H-indol-1-yl]acetic acid in DMF was treated with a dimethylamine hydrochloride (1.05 eq.) and HATU (1.05 eq.). The solution was cooled to 0 °C then treated with DIEA (4 eq.) then stirred for 12 h at 20 °C. The mixture was diluted with AcOEt then washed sequentially with aqueous HCl (1 N), saturated aqueous NaHCO₃ and brine. The dried organic layer was concentrated and the residue was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (90%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.35-1.50 (m, 3H), 1.68-1.75 (m, 3H), 1.80-2.00 (m, 4H), 2.82-2.88 (m, 1H), 2.87 (s, 3H), 3.17 (s, 3H), 3.86 (s, 3H), 5.26 (s, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H); MS (ES⁺) *m/z* 421 (M+H)⁺

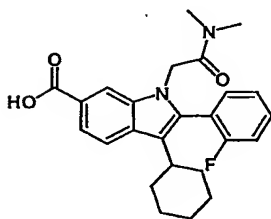


Step 7: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1H-indole-6-carboxylic acid

A solution (0.1 M) of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate in DME and EtOH (5:2) was treated with 4-methylphenylboronic acid (1.2 eq.). Aqueous Na₂CO₃ (2 N, 8.5 eq.) was added and the solution was degassed, then treated with Pd(PPh₃)₄ (0.1 eq.). The mixture was heated at 80 °C for 4 h, then cooled and diluted with AcOEt and brine. The organic phase was separated and dried then

concentrated under reduced pressure. The residue was purified by filtration through silica gel (1:9 AcOEt/petroleum ether) to give a solid that was dissolved in CH₂Cl₂. The resulting solution (0.1 M) was treated dropwise with BBr₃ (3 eq.) then stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was treated with aqueous HCl (1 N) then filtered. Purification by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm) gave the title compound (66%) as a solid.

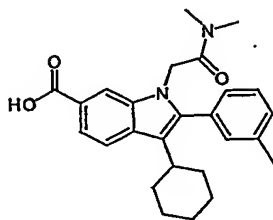
¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.09-1.42 (m, 3H), 1.59-1.99 (m, 7H), 2.41 (s, 3H), 2.48-2.65 (m, 1H), 2.83 (s, 3H), 2.93 (s, 3H), 4.86 (s, 2H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 12.60 (br s, 1H); MS (ES⁺) *m/z* 419 (M+H)⁺



Example 2: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(2-fluorophenyl)-1H-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1H-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate with 2-fluorophenylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm) to afford the title compound (53%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.10-1.40 (m, 3H), 1.60-1.90 (m, 7H), 2.39-2.62 (m, 1H), 2.77 (s, 3H), 2.91 (s, 3H), 4.62 (d, *J* = 17.5 Hz, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 7.26-7.48 (m, 3H), 7.54-7.64 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H); MS (ES⁺) *m/z* 423 (M+H)⁺



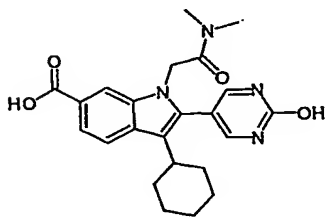
Example 3: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(3-methylphenyl)-1H-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-

- 5 (dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1H-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate with 3-methylphenylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm) to afford the title
- 10 compound (61%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.11-1.41 (m, 3H), 1.60-2.00 (m, 7H), 2.39 (s, 3H), 2.48-2.66 (m, 1H), 2.83 (s, 3H), 2.91 (s, 3H), 4.86 (s, 2H), 7.07-7.20 (m, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 12.60 (s, 1H); MS (ES⁺) *m/z* 419 (M+H)⁺

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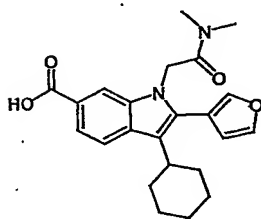
Example 4: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(2-hydroxypyrimidin-5-yl)-1H-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-

- 20 (dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1H-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate with 2-methoxypyrimidin-5-ylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase:

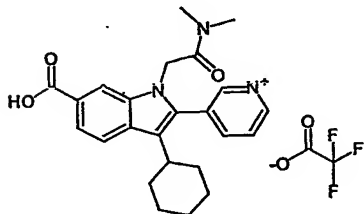
linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 10 min) to afford the title compound (21%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.22-1.40 (m, 3H), 1.62-1.90 (m, 7H), 2.45-2.62 (m, 1H), 2.83 (s, 3H), 3.06 (s, 3H), 5.05 (s, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H), 8.16 (s, 2H); MS (ES⁺) *m/z* 423 (M+H)⁺



Example 5: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(3-furyl)-1H-indole-6-carboxylic acid

- 10 Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1H-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indole-6-carboxylate with 3-furylboronic acid gave a residue that was purified by HPLC (stationary phase: Waters
- 15 Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 11 min) to afford the title compound (25%) as a solid.
- ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.20-1.42 (m, 3H), 1.63-1.95 (m, 7H), 2.65-2.78 (m, 1H), 2.85 (s, 3H), 3.03 (s, 3H), 4.99 (s, 2H), 6.50 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.95 (s, 1H); MS (ES⁺) *m/z* 395 (M+H)⁺
- 20

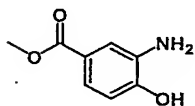


Example 6: 3-{6-carboxy-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1H-indol-2-yl}pyridinium trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-(4-methylphenyl)-1*H*-indole-6-carboxylic acid (step 7), treatment of methyl 2-bromo-3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-indole-6-carboxylate with 2-fluorophenyl boronic acid gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 20% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 10 min) to afford the title compound (23%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.15-1.40 (m, 3H), 1.62-1.92 (m, 7H), 2.45-2.58 (m, 1H), 2.79 (s, 3H), 2.95 (s, 3H), 4.96 (s, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 7.6 and 4.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H) 8.01 (s, 1H), 8.62 (s, 1H), 8.78 (d, *J* = 4.8 Hz, 1H); MS (ES⁺) *m/z* 406 (M+H)⁺

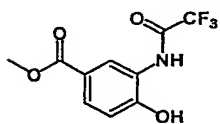
Example 7: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid



Step 1: methyl 3-amino-4-hydroxybenzoate

A solution (0.2 M) of acetyl chloride (3.0 eq.) in MeOH was prepared at 0 °C then allowed to warm to 20 °C. 3-amino-4-hydroxybenzoic acid (1.0 eq.) was added and the mixture was heated under reflux for 12 h then cooled and concentrated *in vacuo*. The residue was triturated with H₂O and dried to afford the title compound (99%) as a solid.

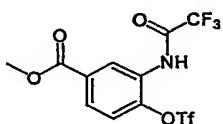
¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 3.83 (s, 3H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 2.1 Hz, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 2.1 Hz, 1H), 11.65 (br s, 1H)



Step 2: methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate

A solution (0.2 M) of methyl 3-amino-4-hydroxybenzoate in THF was cooled to 0 °C and treated dropwise with trifluoroacetic anhydride (2.0 eq.). The mixture was stirred at 0 °C for 2 h then at 20 °C for 1 h. The pH was adjusted to 7.5 by addition of saturated aqueous NaHCO₃ and the solution was extracted with AcOEt. The organic layer was washed with brine and dried, then concentrated to afford the title compound (87%) as a solid.

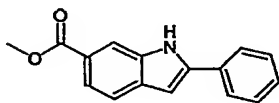
¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 3.82 (s, 3H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.77 (dd, *J* = 2.1 Hz, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 10.82 (br s, 1H)



Step 3: methyl 3-[(trifluoroacetyl)amino]-4-[(trifluoromethyl)sulfonyl]oxybenzoate

A solution (0.8 M) of methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate in dry pyridine was cooled to 0 °C and treated dropwise with trifluoromethanesulfonyl anhydride (1.15 eq.). The mixture stirred for 1 h at 20 °C then diluted with H₂O and AcOEt. The organic layer was separated and washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent afforded a residue that was purified by flash chromatography (1:9 AcOEt/petroleum ether eluent) to afford the title compound (64%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 3.92 (s, 3H), 7.82 (d, *J* = 8.7 Hz, 1H), 8.11 (dd, *J* = 2.2 Hz, *J* = 8.7 Hz, 1H), 8.17 (d, *J* = 2.2 Hz, 1H), 11.81 (s, 1H)

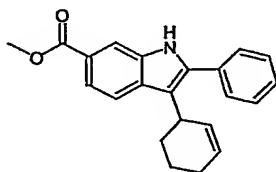


Step 4: methyl 2-phenyl-1H-indole-6-carboxylate

A solution (0.3 M) of methyl 3-[(trifluoroacetyl)amino]-4-[(trifluoromethyl)sulfonyl]oxybenzoate in dry DMF was treated with

ethynyl benzene (2.0 eq.), tetramethyl guanidine (10.0 eq.), PdCl₂(PPh₃)₂ (0.1 eq.) and CuI (0.1 eq.). The mixture was stirred at 20 °C for 1 h then heated at 100 °C for 8 h. The cooled solution was diluted with Et₂O and filtered through Celite. The filtrate was washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent afforded a residue that was purified by flash chromatography (1:9 AcOEt/petroleum ether eluent) to afford the title compound (39%) as a solid.

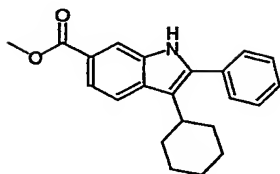
¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 3.88 (s, 3H), 7.04 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.65 (s, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 8.08 (s, 1H), 11.94 (s, 1H)



Step 5: methyl 3-cyclohex-2-en-1-yl-2-phenyl-1H-indole-6-carboxylate

A solution (0.06 M) of methyl 2-phenyl-1H-indole-6-carboxylate in dry DMF was cooled to 0 °C and treated with NaH (1.1 eq.). The mixture was warmed to 20 °C and stirred for 0.5 h, then cooled to 0 °C. A solution (0.3 M) 3-bromocyclohexene (1.3 eq.) in DMF was added dropwise and the mixture was stirred for 2 h at 20 °C. Aqueous HCl (1 N) and AcOEt were added and the organic layer was separated, washed with brine and dried. Removal of the solvent afforded a residue that was purified by flash chromatography on silica gel (1:9 AcOEt/petroleum ether) to afford the title compound (79%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.57-1.74 (m, 1H), 1.82-2.05 (m, 3H), 2.06-2.18 (m, 1H), 2.18-2.32 (m, 1H), 3.67-3.81 (m, 1H), 3.87 (s, 3H), 5.69 (d, *J* = 10.4 Hz, 1H), 5.82-5.92 (m, 1H), 7.44-7.52 (m, 1H), 7.54-7.63 (m, 5H), 7.68 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 11.59 (s, 1H).

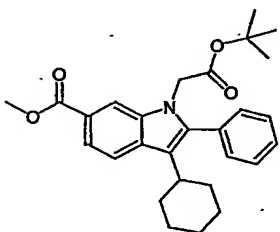


Step 6: methyl 3-cyclohexyl-2-phenyl-1H-indole-6-carboxylate

A solution (0.01 M) of methyl 3-cyclohexyl-2-phenyl-1H-indole-6-carboxylate in MeOH was treated with 10% Pd/C (10% wt.). The resulting

5 suspension was stirred for 12 h under an atmosphere of hydrogen then purged with nitrogen and filtered. The filtrate was concentrated to afford the title compound (91%) as a solid.

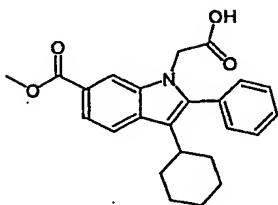
¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.21-1.45 (m, 3H), 1.67-1.90 (m, 5H), 1.91-2.11 (m, 2H), 2.82-2.99 (m, 1H), 3.88 (s, 3H), 7.43-7.52 (m, 1H),
10 7.54-7.60 (m, 4H), 7.62 (dd, *J* = 1.4 Hz, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 11.51 (s, 1H).



Step 7: methyl 1-(2-tert-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1H-indole-6-carboxylate

15 A solution (0.05 M) of methyl 3-cyclohexyl-2-phenyl-1H-indole-6-carboxylate in DMF was treated with NaH (1.4 eq.) then stirred for 0.5 h. *tert*-Butyl bromoacetate (2.0 eq.) was added dropwise, and the mixture was heated at 50 °C for 12 h. After cooling to room temperature the solution was diluted with AcOEt and washed
20 sequentially with aqueous HCl (1 N) and brine. The dried organic phase was concentrated to give a residue that was purified by flash chromatography on silica gel (5:95 AcOEt/petroleum ether) to afford the title compound (83%) as a solid.

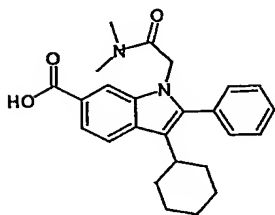
¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.19-1.27 (m, 3H), 1.32 (s, 9H), 1.62-1.95 (m, 7H), 2.59-2.67 (m, 1H), 3.89 (s, 3H), 4.75 (s, 2H), 7.33-7.37 (m, 2H), 7.54-7.57
25 (m, 3H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H).



Step 8: [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1H-indol-1-yl]acetic acid

A solution (0.07 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1H-indole-6-carboxylate in a 1:1 (v/v) mixture of CH₂Cl₂/TFA was stirred for 4 h then concentrated under reduced pressure. The residue was triturated with Et₂O to afford the title compound (98%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.17-1.29 (m, 3H), 1.63-1.75 (m, 5H), 1.68-1.90 (m, 2H), 2.51-2.60 (m, 1H), 3.86 (s, 3H), 4.73 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.51-7.56 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 12.96 (br s, 1H).

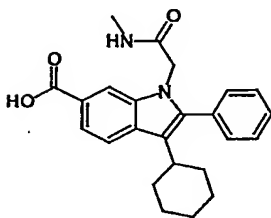


Step 9: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid

A solution (0.04 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1H-indol-1-yl]acetic acid in DMF was treated with dimethylamine hydrochloride (1.0 eq.) and HATU (1.0 eq.). DIEA (3.0 eq.) was added and the mixture was stirred for 12 h. The mixture was diluted with AcOEt then washed sequentially with aqueous HCl (1 N), saturated aqueous NaHCO₃ and brine. The dried organic layer was concentrated and diluted to with CH₂Cl₂. The resulting solution (0.03 M) was treated dropwise with BBr₃ (3 eq.) then stirred for 2 h. The solvent was removed under reduced pressure and the residue was treated with aqueous HCl (1 N) then filtered. Purification by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 40% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 11 min) gave the title compound (70%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.13-1.30 (m, 3H), 1.63-1.75 (m, 5H), 1.80-1.90 (m, 2H), 2.53-2.59 (m, 1H), 2.79 (s, 3H), 2.89 (s, 3H), 4.84 (s, 2H), 7.31 (d, *J* = 6.4 Hz, 2H), 7.48-7.53 (m, 3H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H); MS (ES⁺) *m/z* 405 (M+H)⁺

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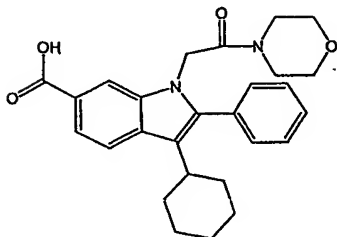


Example 8: 3-cyclohexyl-1-[2-(methylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with methylamine hydrochloride gave a residue that was purified by SPE (stationary phase: Isolute C₁₈ 20g; mobile phase: 10% to 60% MeCN in H₂O) to afford the title compound (51%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.16-1.30 (m, 3H), 1.63-1.73 (m, 5H), 1.80-1.89 (m, 2H), 2.51-2.55 (m, 1H), 2.58 (d, *J* = 4.4 Hz, 3H), 4.51 (s, 2H), 7.38 (d, *J* = 6.4 Hz, 2H), 7.48-7.52 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.98 (d, *J* = 4.4 Hz, 1H); MS (ES⁺) *m/z* 391 (M+H)⁺

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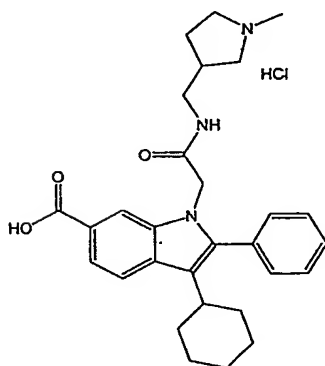
Example 9: 3-cyclohexyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-

25

6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with morpholine (1.2 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 30% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 10 min) to afford the title compound (66%) as a solid.

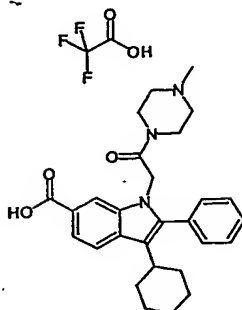
¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.17-1.30 (m, 3H), 1.63-1.77 (m, 5H), 1.80-1.90 (m, 2H), 2.53-2.58 (m, 1H), 3.31-3.39 (m, 8H), 4.89 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.49-7.54 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H); MS (ES⁺) *m/z* 447 (M+H)⁺



Example 10: 3-cyclohexyl-1-(2-((1-methylpyrrolidin-3-yl)methylamino)-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid hydrochloride

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with 1-(1-methylpyrrolidin-3-yl)methanamine (1.2 eq.) gave a residue that was purified by SPE (stationary phase: Isolute C₁₈ 20g; mobile phase: 10% to 70% MeCN in H₂O) to afford the title compound (47%) as a solid.

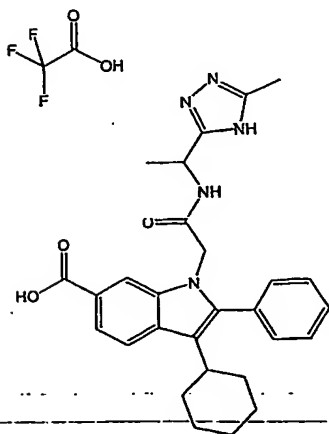
¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.17-1.30 (m, 4H), 1.41-1.50 (m, 1H), 1.63-1.78 (m, 5H), 1.82-1.91 (m, 3H), 2.30-2.39 (m, 1H), 2.45 (s, 3H), 2.53-2.58 (m, 1H), 2.67-2.90 (m, 3H), 3.07-3.09 (m, 2H), 4.54 (s, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.49-7.54 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 3H), 7.83 (d, *J* = 8.4 Hz, 3H), 7.93 (s, 1H), 8.25 (t, *J* = 6.0 Hz, 1H); MS (ES⁺) *m/z* 474 (M+H)⁺



Example 11: 3-cyclohexyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid trifluoroacetate

- 5 Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1H-indol-1-yl]acetic acid with 1-methylpiperazine (1.2 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 10% to 100% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 10 min) to afford the title compound (38%) as a solid.

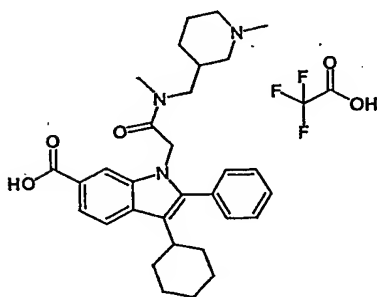
¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.17-1.35 (m, 3H), 1.63-1.73 (m, 5H), 1.80-1.89 (m, 2H), 2.53-2.60 (m, 1H), 2.81 (s, 3H), 2.70-2.97 (m, 4H), 3.18-3.42 (m, 2H), 3.97-4.11 (m, 1H), 4.31-4.40 (m, 1H), 4.88-5.12 (m, 2H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.50-7.55 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H), 9.88 (br s, 1H), 12.50 (br s, 1H); MS (ES⁺) *m/z* 460 (M+H)⁺



Example 12: 3-cyclohexyl-1-(2-{[1-(5-methyl-4*H*-1,2,4-triazol-3-yl)ethyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid with 1-(5-methyl-4*H*-1,2,4-triazol-3-yl)ethanamine dihydrochloride (1.2 eq.) and DIEA (5.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 10 min) to afford the title compound (46%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.15-1.30 (m, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.63-1.73 (m, 5H), 1.82-1.90 (m, 2H), 2.34 (s, 3H), 2.53-2.60 (m, 1H), 4.57-4.63 (m, 2H), 4.94-4.98 (m, 1H), 7.36 (d, *J* = 6.4 Hz, 1H), 7.47-7.51 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 3H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 8.61 (d, *J* = 8.0 Hz, 1H); MS (ES⁺) *m/z* 486 (M+H)⁺

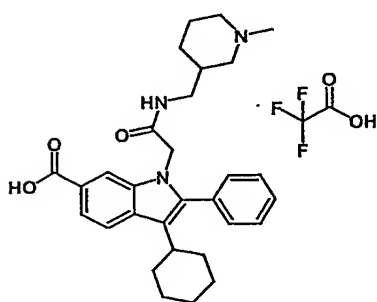


Example 13: 3-cyclohexyl-1-(2-{methyl[(1-methylpiperidin-3-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH₂Cl₂ with *N*-methyl-1-(1-methylpiperidin-3-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from

10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford the title compound (51%) as a solid.

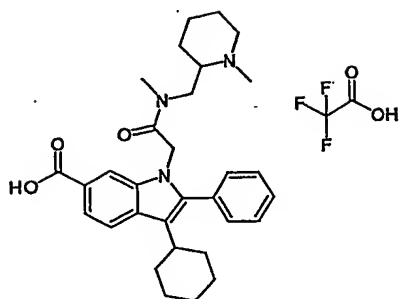
¹H NMR (300 MHz, DMSO-*d*₆, 340 K) δ 1.13-1.41 (m, 3H), 1.47-1.97 (m, 11H), 1.97-2.19 (m, 1H), 2.57-2.71 (m, 1H), 2.78 (s, 3H), 2.94 (s, 3H), 3.04-
5 3.36 (m, 6H), 4.92 (s, 2H), 7.33- 7.50 (m, 2H), 7.53-7.65 (m, 3H), 7.73 (d, *J*
= 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 8.00 (br s, 1H); MS (ES⁺) *m/z* 502
(M+H)⁺



10 **Example 14: 3-cyclohexyl-1-(2-[[1-(1-methylpiperidin-3-yl)methyl]amino]-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate**

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03
15 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH₂Cl₂ with 1-(1-methylpiperidin-3-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90%
MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford
20 the title compound (57%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 340 K) δ 0.98-1.40 (m, 5H), 1.48-2.04 (m, 12H), 2.57-2.70 (m, 1H), 2.84 (s, 3H), 2.97-3.11 (m, 2H), 3.17-3.50 (m, 2H),
4.59 (s, 2H), 7.39- 7.49 (m, 2H), 7.50-7.61 (m, 3H), 7.71 (d, *J* = 8.4 Hz, 1H),
7.84 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 8.06 (t, *J* = 5.0 Hz, 1H), 9.15 (br s,
25 1H); MS (ES⁺) *m/z* 488 (M+H)⁺

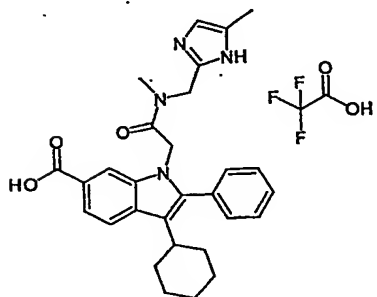


Example 15: 3-cyclohexyl-1-(2-{methyl[(1-methylpiperidin-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1H-indole-6-carboxylic acid trifluoroacetate

- 5 Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1H-indol-1-yl]acetic acid in CH₂Cl₂ with *N*-methyl-1-(1-methylpiperidin-2-yl)methanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary
- 10 phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford the title compound (57%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 340 K) δ 1.12-1.42 (m, 5H), 1.54-1.98 (m, 12H), 2.57-2.70 (m, 1H), 2.79 (s, 3H), 2.96 (s, 3H), 3.11-3.83 (m, 4H), 4.93 (s, 2H), 7.30-7.45 (m, 2H), 7.47-7.61 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H); MS (ES⁺) *m/z* 502 (M+H)⁺

15

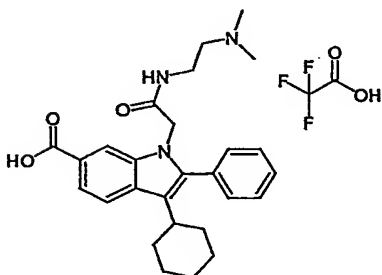


- Example 16: 3-cyclohexyl-1-(2-{methyl[(5-methyl-1H-imidazol-2-yl)methyl]amino}-2-oxoethyl)-2-phenyl-1H-indole-6-carboxylic acid trifluoroacetate**
- 20

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid in CH₂Cl₂ with *N*-methyl-1-(5-methyl-1*H*-imidazol-2-yl)methanamine (1.2 eq.),

- 5 HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford the title compound (65%) as a solid.

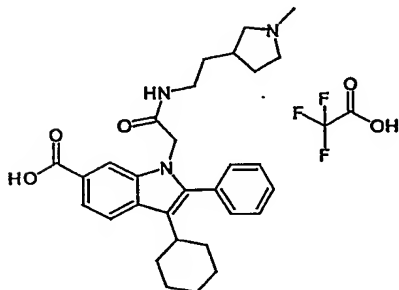
¹H NMR (300 MHz, DMSO-*d*₆, 340 K) δ 1.08-1.39 (m, 3H), 1.55-1.99 (m, 7H), 2.28 (s, 3H), 2.52-2.68 (m, 1H), 3.02 (s, 3H), 4.62 (s, 2H), 4.93 (s, 2H), 7.11- 7.39 (m, 3H), 7.41-7.60 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H); MS (ES⁺) *m/z* 485 (M+H)⁺



- 15 **Example 17: 3-cyclohexyl-1-([2-(dimethylamino)ethyl]amino)-2-oxoethyl-2-phenyl-1*H*-indole-6-carboxylic acid trifluoroacetate**
Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1*H*-indol-1-yl]acetic acid
- 20 in CH₂Cl₂ with *N,N*-dimethylethane-1,2-diamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford the title compound (63%) as a solid.

25 ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.06-1.45 (m, 3H), 1.56-2.03 (m, 7H), 2.51-2.65 (m, 1H), 2.80 (d, *J* = 4.6 Hz, 6H), 3.04-3.19 (m, 2H), 3.35-3.49 (m, 2H), 4.63 (s, 2H), 7.33-7.45 (m, 2H), 7.61-7.48 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H); MS (ES⁺) *m/z* 485 (M+H)⁺

= 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.38 (t, J = 5.4 Hz, 1H), 9.38 (br s, 1H), 12.60 (br s, 1H); MS (ES⁺) m/z 448 (M+H)⁺

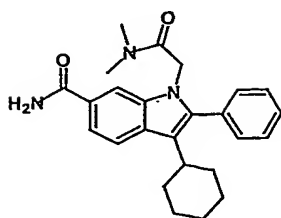


5 **Example 18: 3-cyclohexyl-1-(2-[[2-(1-methylpyrrolidin-3-yl)ethyl]amino]-2-oxoethyl)-2-phenyl-1H-indole-6-carboxylic acid trifluoroacetate**

Following the procedure described above for 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid (step 9), treatment of a solution (0.03 M) of [3-cyclohexyl-6-(methoxycarbonyl)-2-phenyl-1H-indol-1-yl]acetic acid
10 in CH₂Cl₂ with 2-(1-methylpyrrolidin-3-yl)ethanamine (1.2 eq.), HATU (2.0 eq.) and DIEA (6.0 eq.) gave a residue that was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 50 mm; mobile phase: linear gradient from 10% to 90% MeCN (containing 0.1% TFA) in H₂O (containing 0.1% TFA) over 5.5 min) to afford
15 the title compound (64%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.04-1.45 (m, 3H), 1.48-2.13 (m, 13H), 2.14-2.35 (m, 1H), 2.54-2.70 (m, 1H) 2.80 (d, J = 4.9 Hz, 3H), 2.97-3.30 (m, 3H), 3.49-3.68 (m, 1H), 4.59 (s, 2H), 7.36-7.48 (m, 2H), 7.50-7.61 (m, 3H), 7.70 (dd, J = 8.4 Hz, J = 1.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.96
20 (d, J = 1.1 Hz, 1H), 8.28 (t, J = 5.6 Hz, 1H), 9.39 (br s, 1H), 12.64 (br s, 1H); MS (ES⁺) m/z 488 (M+H)⁺

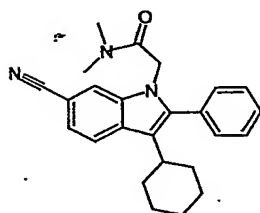
Example 19: 2-[3-cyclohexyl-2-phenyl-6-(1H-tetraazol-5-yl)-1H-indol-1-yl]-N,N-dimethylacetamide



Step 1: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxamide

A solution (0.15 M) of 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxylic acid (prepared as described in example 8) in DMF was treated with pyridine (0.67 eq.), NH_4HCO_3 (1.45 eq.) and di-*tert*-butyl dicarbonate (1.5 eq.). The mixture was stirred for 72 h then diluted with aqueous HCl (1 N) and AcOEt. The organic phase was separated, washed with brine and dried. Removal of the solvent afforded the title compound (67%) as a solid.

^1H NMR (600 MHz, $\text{DMSO}-d_6$, 300 K) δ 1.14-1.36 (m, 3H), 1.61-1.79 (m, 5H), 1.81-1.93 (m, 2H), 2.51-2.60 (m, 1H), 2.81 (s, 3H), 2.92 (s, 3H), 4.80 (s, 2H), 7.20 (br s, 1H), 7.31 (d, $J = 7.1$ Hz, 2H), 7.45-7.54 (m, 3H), 7.60 (s, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.86 (br s, 1H), 7.87 (s, 1H); MS (ES^+) m/z 404 ($\text{M}+\text{H}$)⁺



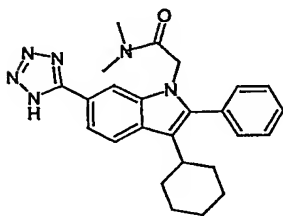
Step 2: 2-(6-cyano-3-cyclohexyl-2-phenyl-1H-indol-1-yl)-N,N-dimethylacetamide

A solution (0.04 M) of 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-indole-6-carboxamide in CH_2Cl_2 was treated with triethylamine (6.4 eq.) and then cooled to 0 °C. Trifluoroacetic anhydride was (3.2 eq.) was added dropwise and the mixture was warmed to 20 °C. After 1 h the solvent was removed and the residue was taken up in AcOEt and aqueous HCl (1 N). The organic layer was separated, washed with brine and dried.

Removal of the solvent gave a residue that was purified by flash

chromatography on silica gel (1:9 AcOEt/petroleum ether) to afford the title compound (90%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.08-1.40 (m, 3H), 1.58-1.97 (m, 7H), 2.51-2.65 (m, 1H), 2.80 (s, 3H), 2.90 (s, 3H), 4.87 (s, 2H), 7.28-7.36 (m, 2H), 7.38 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 2H), 7.48-7.61 (m, 3H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 1.2 Hz, 1H); MS (ES⁺) *m/z* 386 (M+H)⁺

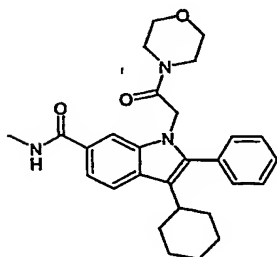


10 Step 3: 2-[3-cyclohexyl-2-phenyl-6-(1H-tetrazol-5-yl)-1H-indol-1-yl]-N,N-dimethylacetamide

A solution (0.02 M) of 2-(6-cyano-3-cyclohexyl-2-phenyl-1H-indol-1-yl)-N,N-dimethylacetamide in toluene was treated with Bu₃SnN₃ (2.0 eq.) and the mixture was heated under reflux for 24 h. The cooled solution was diluted with AcOEt and washed with aqueous HCl (1 N) and then brine. The organic phase was dried and concentrated, and the residue was triturated with pentane to afford a yellow solid.

15 Purification of this material by HPLC (stationary phase: Waters X-terra C₁₈ 19mm x 100 mm) afforded the title compound (45%) as a solid.

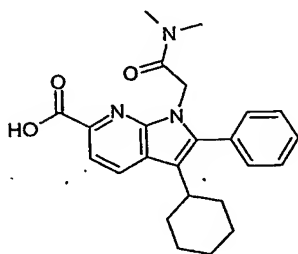
¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 1.14-1.27 (m, 2H), 1.27-1.38 (m, 1H), 1.62-1.70 (m, 1H), 1.70-1.81 (m, 4H), 1.83-1.96 (m, 2H), 2.55-2.63 (m, 1H), 2.82 (s, 3H), 2.93 (s, 3H), 4.86 (s, 2H), 7.33 (d, *J* = 6.6 Hz, 2H), 7.38 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 7.46-7.57 (m, 3H), 7.70 (d, *J* = 8.2 Hz, 1H), 8.97 (d, *J* = 8.2 Hz, 1H), 8.00 (s, 1H); MS (ES⁺) *m/z* 429 (M+H)⁺



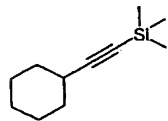
Example 20: 3-cyclohexyl-*N*-methyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxamide

A solution (0.02 M) of 3-cyclohexyl-1-(2-morpholin-4-yl-2-oxoethyl)-2-phenyl-1*H*-indole-6-carboxylic acid (prepared as described in example 10) in CH₂Cl₂ was treated with methylamine hydrochloride (1.2 eq.) and HATU (2.0 eq.). DIEA (6.0 eq.) was added and the mixture was stirred for 12 h. The mixture was diluted with CH₂Cl₂ then washed sequentially with aqueous HCl (1 N), aqueous NaOH (1 N) and brine. The dried organic layer was concentrated and the residue was purified by HPLC (stationary phase: Waters Symmetry C₁₈ 19 mm x 100 mm) to afford the title compound (35%) as a solid.

¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.20-1.38 (m, 3H), 1.70-1.80 (m, 5H), 1.86-1.98 (m, 2H), 2.34 (s, 3H), 2.58-2.68 (m, 1H), 2.88 (d, *J* = 4.5 Hz, 3H), 3.40-3.54 (m, 6H), 3.55-3.60 (m, 2H), 4.89 (s, 2H), 7.37 (d, *J* = 5.7 Hz, 2H), 7.53-7.62 (m, 4H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 8.33 (d, *J* = 4.5 Hz, 1H); MS (ES⁺) *m/z* 460 (M+H)⁺



Example 21: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylic acid



Step 1: (cyclohexylethynyl)(trimethyl)silane

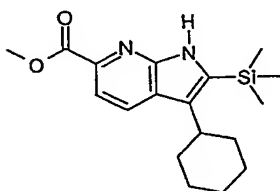
A solution (0.16 M) of 2,2,2-trichloro-1-cyclohexylethyl 4-methylbenzenesulfonate (obtained as described in *J. Org. Chem.*, 65, 1889-1891, 2000) was cooled to -10 °C and a solution of MeLi (1.6 M) was added *via* dropping funnel keeping the

temperature below -5 °C. After the addition the temperature was raised to room temperature over 1 h then the mixture was cooled to -78 °C and treated with TMSCl

(1.7 eq.). After warming to 0 °C the reaction was quenched with saturated aqueous NH₄Cl solution and Et₂O. The organic layer was separated and washed with brine then dried and concentrated to give a crude material which was submitted to fractional distillation. The title compound (63%) distilled off as colorless liquid at 80-82 °C/

5 15-17 mbar.

¹H NMR (300 MHz, CDCl₃, 300 K) 0.33 (s, 9H), 1.14-1.49 (m, 6H), 1.62-1.82 (m, 4H), 2.30- 2.41 (m, 1H)



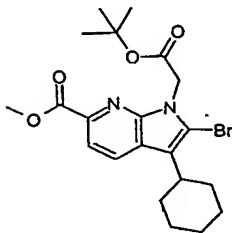
10 Step 2: methyl 3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

To a solution (0.1 M) of methyl 6-amino-5-bromo-2-pyridinecarboxylate (obtained as described in *J. Org. Chem.*, 61, 4623-4633, 1996) in DMF were added

(cyclohexylethynyl)(trimethyl)silane (obtained as described in step 1) (3 eq.), LiCl (1
15 eq.), Na₂CO₃ (2 eq.) and Pd(dppf)Cl₂ (0.1 eq.). The suspension was heated at 110 °C for 15 h under argon, then diluted with AcOEt and H₂O and filtered through celite.

The organics were washed with H₂O and dried, then concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as a pale yellow solid.

20 ¹H NMR (300 MHz, CDCl₃, 300 K) δ 0.39 (s, 9H), 1.39 (m, 3H), 1.82-1.90 (m, 7H), 2.75-2.90 (m, 1H), 4.02 (s, 3H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.53 (br s, 1H); MS (ES⁺) *m/z* 331 (M+H)⁺

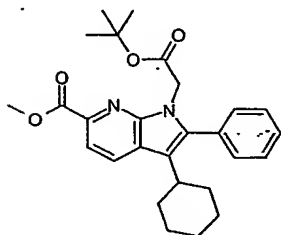


Step 3: methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate

To a solution (0.15 M) of methyl 3-cyclohexyl-2- (trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 2) in DMF was added NaH (1.2 eq.) and the suspension was heated at 40 °C for 15 min under nitrogen. To the resulting clear solution *tert*-butyl bromoacetate (1.3 eq.) was added and the mixture was stirred at 60 °C for 45 min. The reaction was cooled to room temperature, diluted with AcOEt and washed with water, brine, dried and concentrated to give methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate as a pale orange solid.

MS (ES⁺) *m/z* 373 (M+H)⁺. A solution (0.10 M) of this crude material in CH₂Cl₂ was treated with NBS (1.2 eq.) then stirred at 20 °C for 1 h. The solution was diluted with AcOEt and washed with saturated aqueous Na₂S₂O₃ solution and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt /petroleum ether) to afford the title compound (50%) as a white solid.

¹H NMR (400 MHz, CDCl₃, 300 K) δ 1.40-1.46 (m, 2H), 1.47 (s, 9H), 1.81-1.92 (m, 8H), 2.88-2.97 (m, 1H), 4.01 (s, 3H), 5.11 (s, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H); MS (ES⁺) *m/z* 451 (M+H)⁺

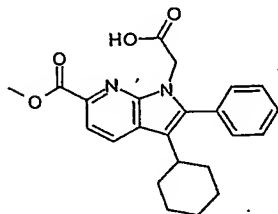


Step 4: methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate

To a solution (0.08 M) of methyl 2-bromo-1- (2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 3) in toluene were added phenylboronic acid (1.5 eq.), potassium phosphate (1.2 eq.), Pd(PPh₃)₄ (0.5 eq.) and the suspension was heated at 110 °C overnight under argon. After cooling to room temperature, the solvent was removed and the residue dissolved in AcOEt and washed with H₂O, brine, dried, concentrated and purified by flash

chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as a pale yellow solid.

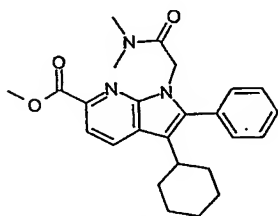
¹H NMR (400 MHz, CDCl₃, 300 K) δ 1.30-1.33 (m, 2H), 1.33 (s, 9H), 1.79-1.85 (m, 8H), 2.61-2.72 (m, 1H), 4.01 (s, 3H), 4.88 (s, 2H), 7.37-7.51 (m, 5H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H); MS (ES⁺) *m/z* 449 (M+H)⁺



Step 5: [3-cyclohexyl-6- (methoxycarbonyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridin-1-yl]acetic acid

A solution (0.06 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1H-pyrrolo[2,3-*b*]pyridine-6-carboxylate (obtained as described in step 4) in CH₂Cl₂/TFA (1:1, v/v) was stirred at room temperature for 1 h. The solvent was removed to afford the title compound (100%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃, 300 K) δ 1.28-1.33 (m, 2H), 1.68-1.82 (m, 8H), 2.61-2.72 (m, 1H), 4.00 (s, 3H), 4.88 (s, 2H), 7.40-7.55 (m, 5H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H); MS (ES⁺) *m/z* 393 (M+H)⁺

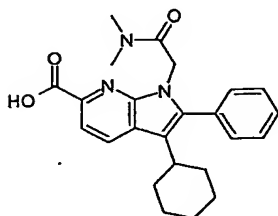


Step 6: methyl 3-cyclohexyl-1- [2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

To a solution (0.05 M) of [3-cyclohexyl-6- (methoxycarbonyl)-2-phenyl-1H-pyrrolo[2,3-*b*]pyridin-1-yl]acetic acid (obtained as described in step 5) in DMF were added dimethylamine hydrochloride (1.1 eq.), HATU (1.2 eq.), DIEA (3.5 eq.) and the solution was stirred at room temperature under nitrogen for 1.5 h. The solution was diluted with AcOEt and washed with aqueous HCl (1 N), aqueous NaOH (1 N) and

brine then dried and concentrated to afford the title compound (100%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃, 300 K) δ 1.28-1.33 (m, 2H), 1.72-1.90 (m, 8H), 2.62-2.68 (m, 1H), 2.88 (s, 3H), 3.02 (s, 3H), 4.01 (s, 3H), 4.97 (s, 2H), 7.43-7.51 (m, 5H),
5 7.93 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H); MS *m/z* (ES⁺) 420 (M+H)⁺

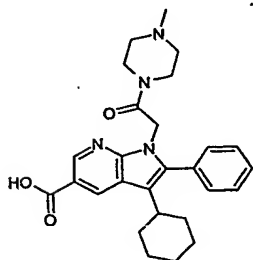


Step 7: 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid

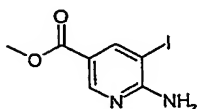
10 To a solution (0.02 M) of methyl 3-cyclohexyl-1-[2-(dimethylamino)-2-oxoethyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (obtained as described in step 6) in CH₂Cl₂ was added neat BBr₃ (3.0 eq.) and the solution was stirred at room temperature under nitrogen for 30 min. The solvent was removed and the residue treated with aqueous HCl (1 N) and purified by preparative HPLC (mobile phase:
15 MeCN/H₂O containing 0.1% TFA) to afford the title compound (45%) as a yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.16-1.35 (m, 3H), 1.63-1.88 (m, 7H), 2.53-2.63 (m, 1H), 2.74 (s, 3H), 2.94 (s, 3H), 4.99 (s, 2H), 7.38-7.58 (m, 5H), 7.85 (d, *J* = 8.2 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H); MS (ES⁺) *m/z* 406 (M+H)⁺

20



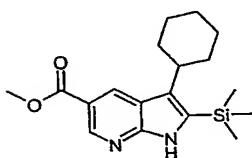
Example 22: 3-cyclohexyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid



Step 1: methyl 6-amino-5-iodonicotinate

To a solution (0.48 M) of methyl 6-aminonicotinate in glacial acetic acid/ TFA (20:1, v/v) was added NIS (1.5 eq.) and the solution was stirred at room temperature overnight. To the solution were added ice, saturated aqueous NH_4OH until pH c. 9 was reached. The precipitate was isolated by filtration, dissolved in CHCl_3 and washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, H_2O and brine then dried and concentrated to afford the title compound (50%) as a solid.

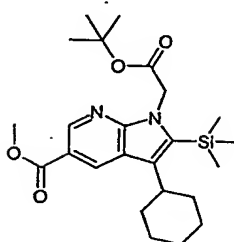
^1H NMR (400 MHz, $\text{DMSO}-d_6$, 300 K) δ 3.77 (s, 3H), 6.90-7.0 (br s, 2H), 8.26 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H); MS (ES^+) m/z 279 ($\text{M}+\text{H}$) $^+$



Step 2: methyl 3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate

To a solution (0.1 M) of methyl 6-amino-5-iodonicotinate (obtained as described in step 1) in DMF were added (cyclohexylethynyl)(trimethyl)silane (obtained as described in example 21, step 1) (3 eq.), LiCl (1 eq.), Na_2CO_3 (2 eq.) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (1 eq.). The suspension was heated in microwave for 10 min at 180 $^\circ\text{C}$, then diluted with $\text{AcOEt}/\text{H}_2\text{O}$ (1/1, v/v) and filtered through celite. The organics were washed with brine and dried then concentrated and purified by flash chromatography on silica gel (AcOEt /petroleum ether) to afford the title compound (20%) as an off-white solid.

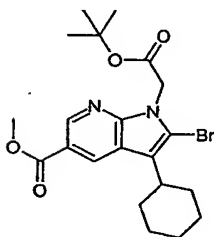
^1H NMR (400 MHz, CDCl_3 , 300 K) δ 0.39 (s, 9H), 1.37-1.45 (m, 3H), 1.80-1.97 (m, 7H), 2.77- 2.85 (m, 1H), 3.97 (s, 3H), 8.71 (s, 1H), 8.93 (s, 1H), 9.04 (br s, 1H); MS m/z (ES^+) 331 ($\text{M}+\text{H}$) $^+$



Step 3: methyl 1-(2-tert-butoxy-2-oxoethyl)-3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate

To a solution (0.16 M) of methyl 3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (obtained as described in step 2) in DMF was added NaH (1.2 eq.) and the suspension was heated at 40 °C for 15 min under nitrogen. To the resulting clear solution *tert*-butyl bromoacetate (1.3 eq.) was added and the mixture stirred at 60 °C for 45 min. After cooling the solution was diluted with AcOEt, washed with H₂O and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (60%) as yellow oil.

¹H NMR (400 MHz, CDCl₃, 300 K) δ 0.39 (s, 9H), 1.37-1.51 (m, 3H), 1.44 (s, 9H), 1.75-1.97 (m, 7H), 2.87-2.98 (m, 1H), 3.95 (s, 3H), 5.08 (s, 2H), 8.66 (d, *J* = 2.0 Hz, 1H), 8.91 (d, *J* = 2.0 Hz, 1H); MS (ES⁺) *m/z* 447 (M+H)⁺

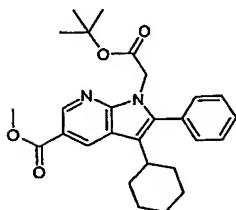


Step 4: methyl 2-bromo-1-(2-tert-butoxy-2-oxoethyl)-3-cyclohexyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylate

To a solution (0.1 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-(trimethylsilyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (obtained as described in step 3) in CH₂Cl₂ was added NBS (2 eq.) and the solution stirred at room temperature for 1 h. The solution was diluted with AcOEt and washed with saturated aqueous Na₂S₂O₃ solution and brine then dried, concentrated and purified by flash

chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (45%) as a white solid.

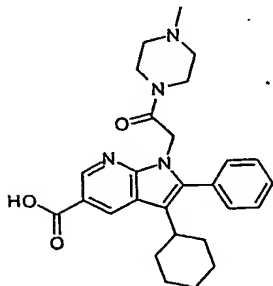
^1H NMR (400 MHz, CDCl_3 , 300 K) δ 1.37-1.48 (m, 3H), 1.42 (s, 9H), 1.75-1.93 (m, 7H), 2.85-2.96 (m, 1H), 3.97 (s, 3H), 5.02 (s, 2H), 8.62 (d, $J = 2.0$ Hz, 1H), 8.90 (d, $J = 2.0$ Hz, 1H); MS (ES^+) m/z 451 ($\text{M}+\text{H}$) $^+$



Step 5: methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate

To a solution (0.08 M) of methyl 2-bromo-1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (obtained as described in step 4) in toluene were added phenylboronic acid (1.5 eq.), potassium phosphate (2 eq.), $\text{Pd}(\text{PPh}_3)_4$ (0.1 eq.) and the suspension was heated at 110 °C overnight under argon. After cooling, the solvent was removed and the residue was dissolved in AcOEt, washed with H_2O and brine then dried, concentrated and purified by flash chromatography on silica gel (AcOEt/petroleum ether) to afford the title compound (70%) as a colorless oil.

^1H NMR (300 MHz, CDCl_3 , 300 K) 1.22 (m, 2H), 1.29 (s, 9H), 1.75- 1.79 (m, 8H), 2.57-2.63 (m, 1H), 3.95 (s, 3H), 4.71 (s, 2H), 7.31- 7.45 (m, 5H), 8.67 (d, $J = 2.0$ Hz, 1H), 8.92 (d, $J = 2.0$ Hz, 1H); MS (ES^+) m/z 449 ($\text{M}+\text{H}$) $^+$

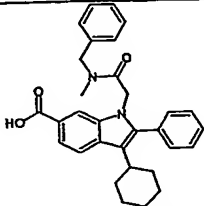
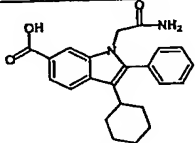
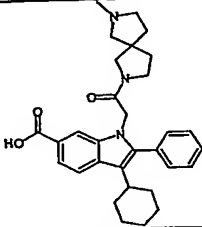
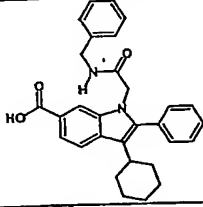
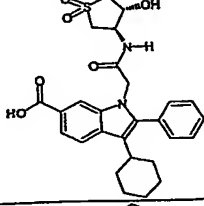
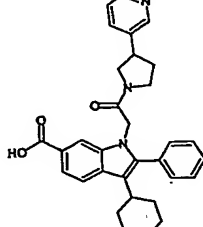
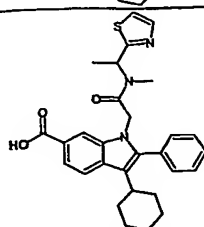


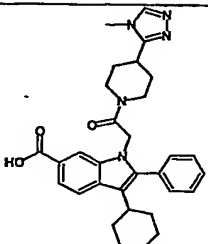
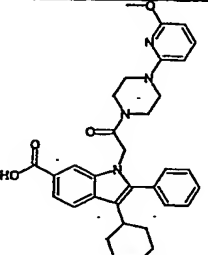
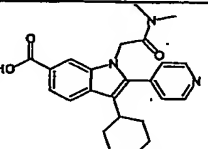
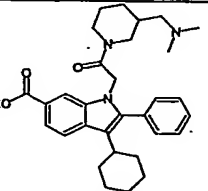
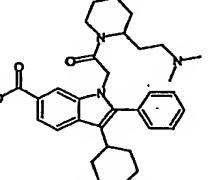
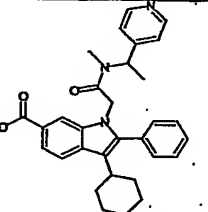
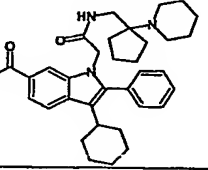
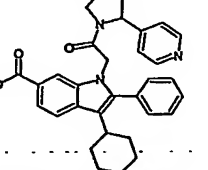
Step 6: 3-cyclohexyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid

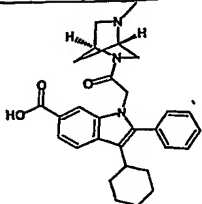
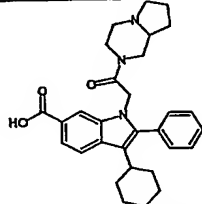
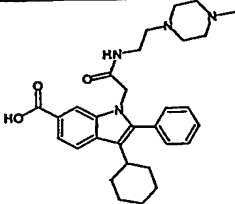
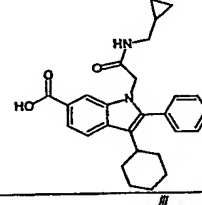
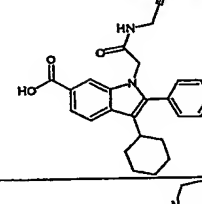
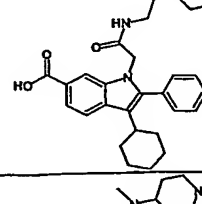
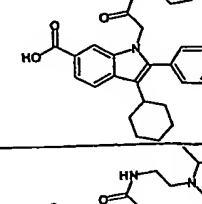
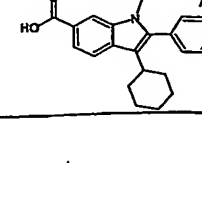
A solution (0.05 M) of methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-cyclohexyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (obtained as described in step 5) in CH₂Cl₂/TFA (1:1, v/v) was stirred at room temperature for 1 h. The solvent was removed to give [3-cyclohexyl-5-(methoxycarbonyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]acetic acid (100%). To a solution (0.09 M) of this material in DMF were added N-methylpiperazine (1.5 eq.), HATU (1.2 eq.), DIEA (3.0 eq.) and the resulting mixture was stirred at room temperature under nitrogen for 1.5 h. The solution was diluted with AcOEt and washed with saturated aqueous NH₄Cl solution, H₂O and brine then dried and concentrated to give methyl 3-cyclohexyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate as a red oil. This material was dissolved in THF (0.18 M) and aqueous KOH (1 N, 3 eq.) was added. The solution was stirred overnight at room temperature then adjusted to pH 3 by addition of aqueous HCl (1 N). The solution was diluted with MeCN/H₂O and purified by preparative HPLC (mobile phase: CH₃CN /H₂O containing 0.1% TFA) to afford the title compound (50%) as a solid.

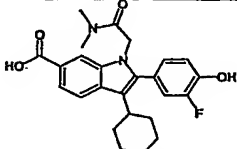
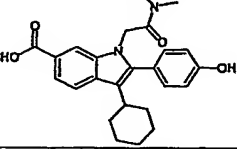
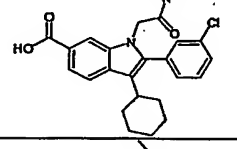
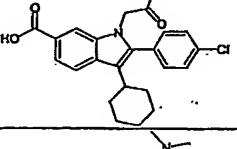
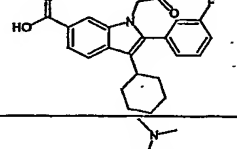
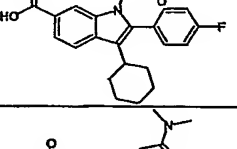
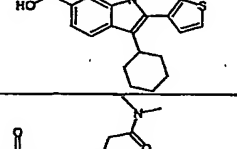
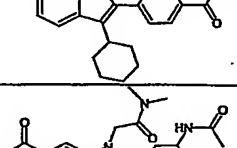
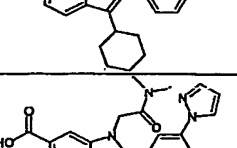
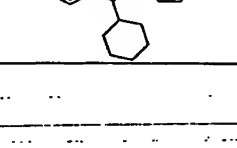
¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 1.19-1.33 (m, 3H), 1.66-1.68 (m, 1H), 1.77-1.82 (m, 6H), 2.59-2.61 (m, 1H), 2.79 (br s, 6H), 4.09-4.27 (m, 2H), 4.97-5.08 (m, 2H), 7.36-7.38 (m, 2H), 7.51-7.56 (m, 3H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.79 (d, *J* = 1.7 Hz, 1H), 9.8 (br s, 1H); MS (ES⁺) *m/z* 461 (M+H)⁺

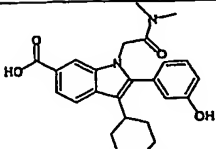
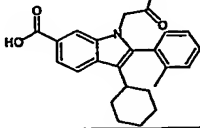
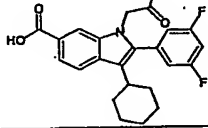
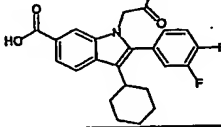
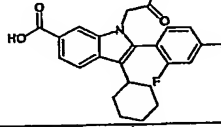
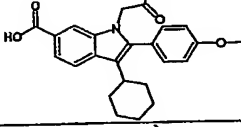
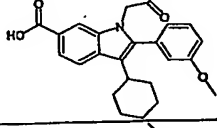
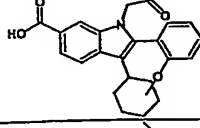
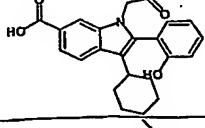
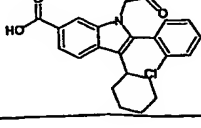
5 **Table 1. Additional Examples (C-6 carboxylic acids)**

STRUCTURE	Molecular Ion [M+H] ⁺
	481
	377
	500
	467
	511
	508
	502

	526
	553
	406
	502
	516
	496
	542
	508

	472
	486
	503
	431
	415
	490
	486
	504

	439
	421
	439
	439
	423
	423
	411
	448
	462
	471

	421
	419
	441
	441
	441
	435
	435
	435
	421
	439

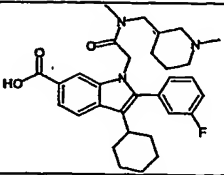
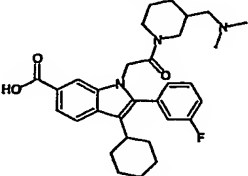
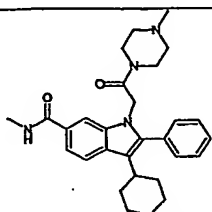
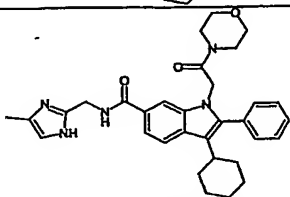
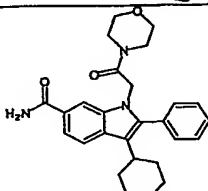
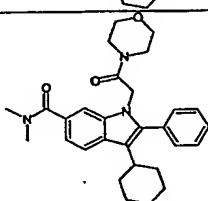
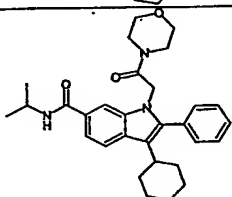
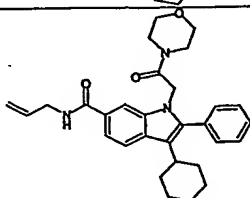
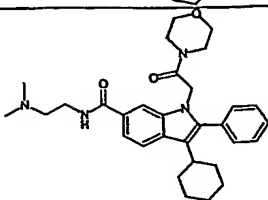
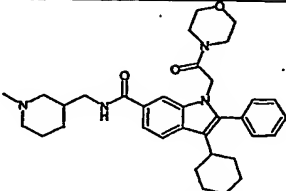
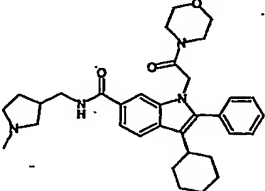
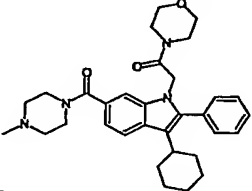
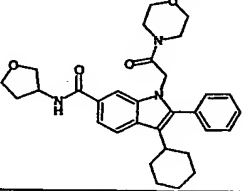
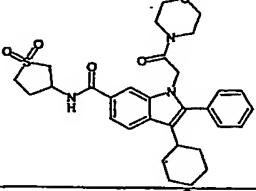
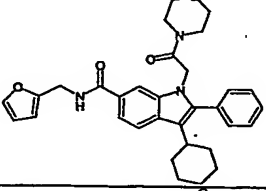
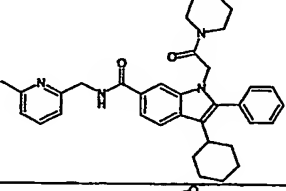
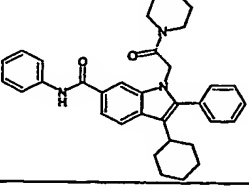
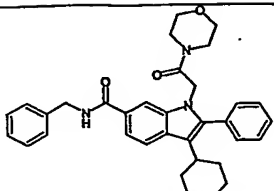
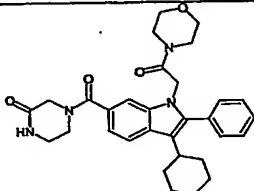
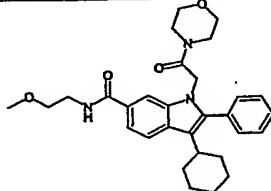
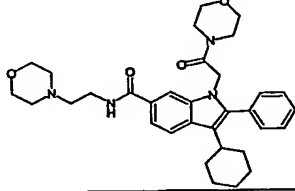
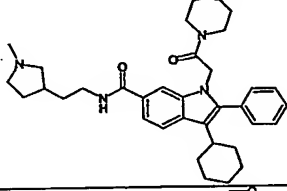
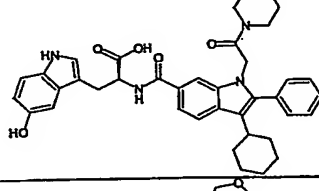
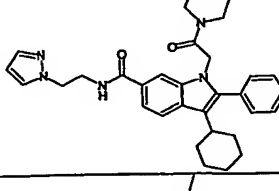
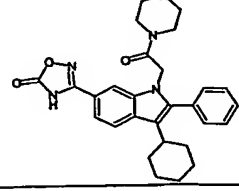
	520
	520

Table 2. Additional Examples (C-6 Carboxamides / Acid Replacements)

STRUCTURE	Molecular Ion [M+H] ⁺
	473
	540
	446
	474
	488
	486
	517

	557
	543
	529
	516
	564
	526
	551
	522

	536
	529
	504
	559
	557
	649
	540
	500

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